A STUDY OF SCREENING COLONOSCOPY IN NON ALCOHOLIC FATTY LIVER DISEASE

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CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY OF SCREENING COLONOSCOPY IN NON ALCOHOLIC FATTY LIVER DISEASE",** submitted by **B.PRAKASH SHANKAR** to the faculty of Medical Gastroenterology, The Tamilnadu Dr.MGR Medical University, Guindy, Chennai-600032, in partial fulfillment of the requirement for the award of DM Degree, Branch IV (Medical Gastroenterology) is a bonafide work carried out by him under my direct supervision and guidance.

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“A STUDY OF SCREENING COLONOSCOPY IN NON ALCOHOLIC FATTY LIVER DISEASE”

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INTRODUCTION

Over half a century ago researchers started to recognize the association between obese population and the presence of hepatic steatosis.[1] Initially it was thought to be a relatively benign entity, but reports started emerging later which suggested that in some circumstances fat in the liver could lead to cirrhosis or liver failure. This was better elicited in patients who undergo surgical jejunoileal bypass for morbid obesity.[2]

The histological features of "fatty liver disease" resemble alcohol-induced liver injury, but because they occur in patients with little or no alcohol consumption, the term Non alcoholic fatty liver disease (NAFLD) was coined.[3,4] NAFLD encompasses a spectrum of diseases that ranges from bland hepatic steatosis, which is generally believed to be a benign condition, to hepatic steatosis with a necroinflammatory component that may or may not have associated fibrosis. This latter condition is termed Non alcoholic steatohepatitis (NASH)[4] and is considered the 'progressive' form of NAFLD.[5]

The natural history and progression of NASH to cirrhosis is unclear with prevalence rates of 3% to 15% in case series[6-8]and small

prospective cohorts have shown that NASH may progress to cirrhosis in 9% to 20% of patients.[9-11]

The pathogenesis of fatty liver disease and NASH is yet to be fully elucidated, but the common association with visceral obesity, hyperlipidemia, hypertension, and diabetes mellitus suggests that it is the hepatic manifestation of the metabolic syndrome,[12] with at least 1 of these features present in over 90% of NAFLD patients.

In Europe and North America colon cancer is the second most common cause of cancer death and is also one of the commonest causes of cancer deaths throughout the worldwide. There are established risk factors like old age, black race, low fiber diets and smoking. There are some potential risk factors like insulin resistance and metabolic syndrome as well. Metabolic syndrome is considered to be present when three of the following parameters are present.

1. Increased waist circumference,
2. Hypertriglyceridemia (triglycerides ≥150 mg/dl),
3. Low high-density lipoprotein
4. HDL cholesterol (≤50 mg/dl in women and ≤40 mg/dl in men),
5. Hypertension (130/ ≥85 mmHg), and
6. Impaired fasting glucose.

Metabolic syndrome is a sequel of conditions that has plagued the world population. Its incidence is fast increasing in populations that are obese and also in overweight people.

Both cardiovascular lesions and malignancies have a common risk factor which is universal in prevalence. That common risk factor is insulin resistance. The insulin resistance syndrome has five basic criteria. They are hyperglycemia, visceral obesity, Hypertriglyceridemia, low HDL-cholesterol level and hypertension. All these conditions are individual risk factors for malignancies, and together they mean multiple risks. Insulin resistance of various organs like liver, fatty tissues and skeletal muscles causes reactive hyperinsulinemia, by the increased secretory activity of the beta-cells. Insulin is a growth factor with diverse metabolic effects. It predisposes to the increased production and mitogenic activity of several insulin-like growth factors, and precipitates pathological cell proliferation. Insulin resistance predisposes to hyperglycemia. Hyperglycemia appears promotes tumor genesis by various pathways. The elevated serum glucose level is contributory to the increased DNA synthesis of the tumor cells. Hyperglycemia leads to production of free radicals and non glycation end products which are all risk factors for the development of neoplasia. Metabolic syndrome and insulin resistance are associated with a higher risk of colon cancer. Non-

alcoholic fatty liver disease (NAFLD) is regarded as a manifestation of metabolic syndrome in the liver[11].

Though colorectal neoplasms are relativey rare in India when compared with the western world, the incidence rate is on the rise due to westernization. The low incidence of colorectal neoplasm in India is thought to be because of the high fiber content of the diet which increases the bulk of the stool thereby dramatically decreasing the intestinal transit time. The rapid intestinal transit is proposed to be a favorable factor, reducing the contact time between the carcinogenic substances present in the stool and the intestinal lumen. However this concept is yet to be proved scientifically.

Overall incidence of colorectal adenomas in people living in tropical countries is much lower than the frequency with which the colorectal adenomas are detected in the western population. However the risk factors like obesity, insulin resistance and metabolic syndrome etc are rising at a staggering rate in tropical countries. Especially in India the metabolic syndrome is considered to be a new age epidemic affecting all ages of population. Metabolic syndrome is considered to be the clinical manifestation of insulin resistance. The insulin resistance is a risk factor for colorectal adenomas.

According to the epidemiological studies colonic adenomas are more common in patients who are obese, African American and with positive family history of colon cancer, or diabetes mellitus. Newer studies have shown that impaired glucose tolerance, dyslipidemia, and metabolic syndrome are also associated with increased risk of colonic adenomas. Patients with nonalcoholic fatty liver disease (NAFLD) often share many of the previously mentioned risk factors for colonic adenomas. We need more studies to assess the relationship between NAFLD and colonic adenomas.

There are few studies from Europe, North America and East Asia analyzing the incidence of colorectal adenomas in people with Non alcoholic fatty liver. However such studies are lacking in India where the incidence of both metabolic syndrome as well as non alcoholic fatty liver disease is increasing. In this study we have compared the incidence rate of colorectal adenomas in patients with Non alcoholic fatty liver with that of patients without Non alcoholic fatty liver.

REVIEW OF LITERATURE

Ludwig et al first coined the term NASH in 1980,[12] Since then the prevalence of NAFLD has risen rapidly along with the rapid rise in prevalence of obesity and diabetes.[13] At present NAFLD is the most common cause of liver disease in the Western world.[14] Non alcoholic fatty liver disease represents a spectrum of diseases encompassing simple steatosis to steatohepatits and fibrosis. Later on some patients with NAFLD go on to develop cirrhosis.

In spite of recent advances, especially in elucidating the complex metabolic and inflammatory pathways that lead to the development of NAFLD, we lack knowledge about the exact pathogenesis of hepatic steatosis and its progression to steatohepatitis and cirrhosis.[15,16] Steatosis is found to be a condition with relatively benign prognosis,[17] However it may be associated with factors that are associated with progression to more advanced, clinically relevant disease. Those factors are inflammatory cytokines/adipokines, mitochondrial dysfunction and oxidative stress.[18]

Insulin resistance is found to be the underlying cause of several conditions like obesity, metabolic syndrome as well as NAFLD.

Insulin resistance leads to adipose tissue lipolysis, which causes increased efflux of free fatty acids (FFA) from adipose tissue to the liver.[19] Hyperinsulinaemia also promotes hepatic de novo lipogenesis, which is markedly increased in NAFLD patients compared with normal individuals.[20] It is now recognized that FFA promote insulin resistance, inflammation and oxidative stress,[21,22] and thus rather than being harmful, hepatic triglyceride accumulation may actually be protective by preventing the harmful effects of FFA.[23] Oxidative stress mechanisms, pro-inflammatory cytokines such as TNF alpha and interleukin 6, and Adipokines such as Leptin (pro inflammatory and pro-fibrotic), and Adiponectin (anti-inflammatory and insulin-sensitising) are also found to be involved in promoting NASH.[16]

Only few percent of patients with NAFLD progresses to NASH which means that there are several other factors which interplay along with underlying genetic predisposition.[15,18]

Causes of NAFLD

In most of the cases the NAFLD seem to occur in association with conditions like insulin resistance, glucose intolerance or diabetes, central obesity, dyslipidemia and hypertension. Thos with alcohol consumption

greater than 20 gm per day are excluded from the diagnosis of NAFLD. Other causes of steatosis are

1. Rapid weight loss
2. Total parenteral nutrition,
3. Rare metabolic disorders
4. Drug-induced Steatosis.
5. Hepatitis C, particularly genotype 3,
6. Endocrine disorders.

Epidemiology

In western adults prevalence of NAFLD ranges from 20% and 30%,[25,26] reaching upto 90% in the morbidly obese.[27] NASH, has an estimated prevalence of 2–3% in the general population and 37% in the morbidly obese.[27] NASH is much more clinically relevant than NAFLD. NAFLD affects 3% of children, with a significant rise up to 53% in obese children,[28,29] which can tremendously increase the future disease burden. 70% of type 2 diabetes population seems to have steatosis.[30]

Non-alcoholic fatty liver disease is prevalent in all races. However it seems to be more common among Hispanics and whites when

compared to African Amercian. This difference remains after controlling for insulin resistance and obesity[25,31] and ethnic differences in lipid metabolism is found to be the contributing factor.[25]

Pathogenesis

The pathogenesis of nonalcoholic fatty liver disease (NAFLD) is multifactorial and its progression is related to several factors. The natural history is influenced by both environmental and genetic factors.[32, 33]

In spite of the inadequate knowledge about the pathogenesis, a 2-hit hypothesis is proposed,[34]

1. First hit; An imbalance of fatty acid metabolism that leads to hepatic triglyceride accumulation (steatosis).

2. Second hit; Oxidative or metabolic stress and dysregulated cytokine production.

This act sequentially, leading to subsequent inflammation and fibrosis.

Hepatic mitochondrial dysfunction is very important in the pathogenesis of NAFLD.[35]

However, the 2-hit hypothesis was recently subjected to debate. With the understanding of the deleterious effects of peripheral and hepatic insulin resistance, the concept of multiple hits is being considered. Despite lack of knowledge about specific pathways leading to inflammation and fibrosis, there are evidences which seem to support a role for dysregulated lipid partitioning which is proposed to be mediated by insulin resistance leading to altered cytokine profiles.

Moreover, the capacity of the liver to repair and recover from injury appears variable and this may change the rate of progression, and also the severity of liver disease.[36]

Microscopic Features

The major histologic features of NAFLD resemble those of alcohol-induced liver disease and include steatosis (fatty liver), steatohepatitis (fatty liver plus parenchymal inflammation with or without accompanying focal necrosis), and varying degrees of fibrosis, including cirrhosis. Steatosis is predominantly macrovesicular and usually is distributed diffusely throughout the liver lobule, although prominent microvesicular steatosis and zone 3 (perivenular) steatosis have been reported occasionally. Mild lymphocytic, neutrophilic, or mixed

inflammatory infiltrates also may be observed, and glycogenated nuclei are common.

NASH, which is an advanced form of NAFLD, is indistinguishable histologically from alcoholic hepatitis. The generally accepted minimal criteria for the diagnosis of nonalcoholic steatohepatitis (NASH) are steatosis, ballooning degeneration, and lobular inflammation.[37, 38] Alternatively, portal inflammation may represent more progressive disease, as shown by Brunt and colleagues.[40] Steatosis is present in all cases and can affect the hepatic lobules either diffusely or primarily in the central zones. The degree of steatosis may correlate with the patient's BMI and generally is more severe in NASH than in alcoholic hepatitis. Lobular inflammation is a hallmark feature of NASH and is characterized by infiltration of lymphocytes, other mononuclear cells, and polymorphonuclear neutrophils. The intensity of the inflammation varies with the severity of steatohepatitis and may be milder in NASH than in alcoholic hepatitis. Glycogenated nuclei may be present. Hepatocyte ballooning and hepatocyte necrosis of varying degrees are present and may portend a worse prognosis. Mallory (or Mallory-Denk) bodies, which may be small, sparse, and inconspicuous, are seen frequently. Mild stainable iron may be present in up to 50% of the patients. Pericellular, perisinusoidal, and periportal fibrosis has been described in 37% to 84%

of patients with NASH. The extent of fibrosis varies considerably, ranging from delicate strands surrounding small veins or groups of cells to densely fibrotic septa with distortion of the hepatic architecture. Perisinusoidal fibrosis is most common, especially in adults, is initially mild, and predominates in zone 3 around the terminal hepatic veins.[41] Cirrhosis is found on initial biopsy in 7% to 16% of patients with NAFLD and abnormal liver biochemical test levels. The risk of cirrhosis in the setting of NAFLD may be greatest in morbidly obese patients. In NAFLD-associated cirrhosis, the typical histologic features of NAFLD may be minimal or absent, potentially leading to the misdiagnosis of cryptogenic cirrhosis.

Immunohistochemistry

p62 or ubiquitin immunostains are useful in NAFLD. Loss of keratin 8/18 immunostaining helps to identify Mallory denk bodies, especially in patients with ballooned hepatocytes and patients with nonalcoholic steatohepatitis (NASH). But, this is nonspecific and may also be seen in patients with alcoholic steatohepatitis and patients with cholestasis or ischemia[41].

Clinical suspicion of NAFLD should be entertained in patients with obesity, obstructive sleep apnea and diabetes mellitus**.** Other liver

diseases that have to be ruled out before making a diagnosis of NAFLD are listed below:

1. Viral hepatitides,
2. Excess alcohol consumption,
3. Hemochromatosis,
4. Autoimmune hepatitis,
5. Wilson's disease
6. Alpha-1 antitrypsin deficiency,
7. Drug-induced liver injury.

Most of patients with NAFLD are asymptomatic and the condition is suspected following elevated transaminases on routine testing. Hepatic steatosis is a frequent incidental finding on ultrasound scan (USG) performed during evaluation for conditions like suspected gallstone disease. Right upper quadrant discomfort and fatigue are the two commonest symptoms, although the latter may be present in Obstructive sleep apnea (OSA). Hepatomegaly is common, with signs of chronic liver disease being conspicuous by its absence. In a recent study it was found that increased dorsocervical lipohypertrophy is associated with severity of steatohepatitis among the anthropometric measures.

Usually NAFLD is suspected in asymptomatic patients with elevation in liver enzymes. However the entire spectrum of NAFLD can present in patients with normal AST(aspartate amino tranferase) and ALT(alanine amino transferase) levels.ALT levels are usually greater than the AST levels. Alkaline phosphatase can be slightly elevated but is rarely the only liver function test abnormality. Gamma-glutamyltransferase (GGT) is increased frequently and can be a marker of increased mortality. Low albumin, hyperbilirubinaemia etc may be indicative of advanced liver disease and are not specific features of NAFLD.

An elevated ferritin is seen in half of the patients and elevated transferrin saturation in about 10%. However, these findings have no correlation with elevated hepatic iron concentration, and its role in the pathogenesis of NASH remains unclear.

Prediction of fatty liver in general population by ultrasound is done using the Fatty Liver Index (FLI).[42] An accuracy of 0.84 in detecting fatty liver was achieved with FLI.[42] FLI has been commonly used by several groups in population studies of NAFLD.[43–45] The commonly used test in patients with suspected NAFLD, with steatosis is Ultra sonogram (USG) which typically shows a hyperechogenic liver. A recent

study which compared USG with the liver biopsy in 235 patients with suspected fatty liver disease showed a sensitivity of 64% and specificity of 97% for USG in patients with less than 30% steatosis, rising to 91% and 93% respectively in patients with at least 30% steatosis.[46] However, sensitivity and specificity of USG is reduced by morbid obesity.[47] and also it is unable to quantify the amount of fat present or provide any staging of disease,[48] and is operator-dependent with significant intra- and inter-observer variability.[49]

Liver imaging

Liver imaging plays an important role in the clinical evaluation of NAFLD and in epidemiologic studies of the disease. However, conventional techniques are unable to grade or stage NASH and are insensitive to hepatic fat that is less than 20% by weight. Cross-sectional imaging is also used to assess fat distribution (visceral versus peripheral fat) by determining the fat area at specific levels such as L4–5. Ultrasonography detects steatosis by echogenicity and sound attenuation with defined criteria . Ultrasonic elastography measures liver stiffness as a marker of fibrosis. Sensitivity and specificity for stage 3–4 fibrosis is 91% and 75%, respectively (>7.9 kPa) but failure to acquire a signal increases with a BMI of >30 kg/m2. Unenhanced computed tomography

(CT) relies on attenuation differences between the liver and spleen. A "liver: spleen ratio" (in Hounsfield units) of <1 is consistent with steatosis. Sensitivity and specificity for fatty liver were 84% and 99%, respectively, for a spleen minus liver value of ≥10 Hounsfield units in one study. Conventional spin-echo magnetic resonance imaging (MRI) is insensitive in detecting steatosis. However, refinements including "in–out of phase imaging" improve fat detection. Improved signal processing (using the Dixon technique) provides quantitative estimates expressed as percentage triglyceride content. Magnetic resonance proton spectroscopy is the most accurate means of quantifying steatosis. In one study, the correlation between fat measured in liver biopsies and proton spectroscopy was 0.9 (P <0.001).

Role of liver biopsy

Liver biopsy remains the standard for confirming the diagnosis, staging fibrosis, grading activity, and judging response to treatment. Clinically, biopsy is often deferred until failure of a conservative course of exercise and diet unless the evaluation indicates more advanced disease or when there is a question of medication-induced injury. Limitations and risks inherent to biopsy have led to study of noninvasive "surrogate" markers.

The limitations of biopsy include risk, patient inconvenience, performance in obese patients, and sampling error. Although always warranting careful caution, complications with liver biopsy are low and available techniques offer improved safety. Sampling error is well recognized with all types of liver biopsy and may represent regional variation within the liver.

Metabolic syndrome and Insulin resistance

In 1988, Reaven described several risk factors like, dyslipidemia, hypertension, hyperglycemia clustering together to form a clinical syndrome. Syndrome X is the name given by him. Reaven and subsequently others postulated that insulin resistance underlies Syndrome X (hence the commonly used term insulin resistance syndrome).Later on other researchers coined the term Metabolic syndrome to describe the same entity which was endorsed by ADULT TREATMENT PANEL III (ATP III).

This entity called as Metabolic syndrome predisposes to following conditions namely

1. Cardiovascular Disease

2. Type 2 diabetes

3. Polycystic ovary syndrome,

4. Fatty liver,

5. Cholesterol gallstones,

6. Asthma,

7. Sleep disturbances

8. Some forms of cancer.

Components of Metabolic Syndrome

According to ATP III the following components of the metabolic syndrome are related to CVD:

1. Obesity which is predominantly abdominal

2. Dyslipidemia predisposing to atherogenic state

3. Elevated blood pressure

4. Impaired glucose intolerance

5. Proinflammatory state

6. Prothrombotic state

ATP III further classified the risk factor into underlying, major, and emerging risk factors.

Underlying risk factors are

1. obesity (especially abdominal obesity),
2. Physical inactivity, and
3. Atherogenic diet;

The major risk factors are

1. Cigarette smoking
2. Hypertension,
3. Elevated LDL cholesterol, low HDL cholesterol,
4. Family history of premature coronary heart disease (CHD),
5. Aging;

The emerging risk factors are

1. Elevated triglycerides,
2. Small LDL particles,
3. Insulin resistance,
4. Glucose intolerance,

5. Proinflammatory state, and Prothrombotic state.

There are several criteria used for diagnosing metabolic syndrome like ATP III guidelines, WHO guidelines, AACE clinical criteria etc

Risk Factor	Defining Level
Abdominal obesity, given as waist circumference*†	
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥110 mg/dL‡

Table 1.ATP III Guidelines for diagnosing Metabolic Syndrome (3 out of 5 risk factors needed

PATHOGENESIS OF METABOLIC SYDROME IN RELATION TO INSULIN RESISTANCE

In the pathogenesis of metabolic syndrome insulin resistance seems to play a more decisive role than obesity. Researchers claim that insulin resistance, or its accomplice, hyperinsulinemia, predisposes to other metabolic risk factors. However since insulin resistance is linked to obesity it is difficult to evaluate the unique role of insulin resistance in patients with metabolic syndrome.

Though Insulin resistance rises with increasing body fat content, a broad range of insulin sensitivities exists at any level of body fat. Most people with categorical obesity (body mass index [BMI ≥30 kg/m2) have postprandial hyperinsulinemia and relatively low insulin sensitivity, but variation in insulin sensitivities exists even within the obese population. Spectrum of insulin sensitivities varies within patients who are overweight (BMI 25 to 29.9 kg/m2), probably due to some inherited component to insulin resistance.

In South Asians, especially Indians, insulin resistance occurs commonly even with BMI ≥25 kg/m2 and which probably contributes to a high prevalence of type 2 diabetes and premature CVD. This entity of insulin resistance in only mild-to-moderate overweight people can termed as primary insulin resistance.

Also in primary insulin resistance, weight gain leads to enhanced insulin resistance and metabolic syndrome. Hence it is difficult to dissociate obesity and primary insulin resistance in patients with metabolic syndrome.

Hyperinsulinemia predisposes to enhanced release of very low-density lipoprotein triglycerides, which will raise the serum triglycerides. Insulin resistance in muscle leads to impaired glucose intolerance, which

can be precipitated by increased hepatic gluconeogenesis. Finally, insulin resistance may also elevate blood pressure by several mechanisms.

Colorectal adenomas

Colonic polyps may be divided into two major groups: neoplastic (the adenomas and carcinomas) and non-neoplastic. The adenomas and carcinomas share a characteristic—cellular dysplasia—but they may be subdivided according to the relative contribution of certain microscopic features. The non-neoplastic polyps may be grouped into several distinct categories: hyperplastic polyps (including serrated polyps), “mucosal polyps,” juvenile polyps, Peutz-Jeghers polyps, inflammatory polyps, and others. Sub mucosal lesions also can impart a polypoid appearance to the overlying mucosa and therefore are briefly mentioned even though they are not true polyps.

Adenomatous polyps are tumors of benign neoplastic epithelium that can either be pedunculated (i.e., attached by a stalk) or sessile (i.e., attached by a broad base with little or no stalk). The neoplastic nature of adenomas is apparent by histological examination of their glandular architecture. Tubular adenomas are the most common subgroup and are characterized by a complex network of branching adenomatous glands. In villous adenomas, the adenomatous glands extend straight down from the

surface to the center of the polyp, thereby creating long, finger-like projections. Tubulovillous (villoglandular) adenomas manifest a combination of these two histological types.

A polyp is assigned a histological type on the basis of its predominant glandular pattern, and in practice, pure villous adenomas are quite rare. According to the World Health Organization, adenomas are classified as tubular if at least 80% of the glands are of the branching, tubule type and as villous if at least 80% of the glands are villiform. Of all adenomatous polyps, tubular adenomas account for 80% to 86%, tubulovillous for 8% to 16%, and villous adenomas for 3% to 16%. Tubular adenomas usually are small and exhibit mild dysplasia, whereas villous architecture is more often encountered in large adenomas and tends to be associated with more severe degrees of dysplasia.

Adenomas are categorized into three size groups: less than 1 cm, 1 to 2 cm, and greater than 2 cm. Overall, most adenomas are smaller than 1 cm, but the size distribution of adenomas can vary greatly among studies, depending on study design, age of the study population, and location of the adenomas within the colon. Thus, in autopsy series, which describe a presumably asymptomatic population dying of other causes, only 13% to 16% of adenomas are larger than 1 cm, whereas surgical and

colonoscopic series that include symptomatic or higher-risk patients report a higher prevalence (26% to 40%) of adenomas larger than 1 cm. In countries where the prevalence of colon cancer is high, adenomas tend to be larger than in low-prevalence countries. Adenoma size increases as a function of age, even in low-prevalence countries, and larger adenomas are more common in distal colonic segments.

In Western countries, colonic polyps are usually adenomatous in nature, are evenly distributed along the entire colon in asymptomatic persons, and show a left-sided predominance in symptomatic patients. There is dearth of such literature from India.

In Western society, the prevalence of adenomas shows a close association with risk of development of colonic carcinoma. In Hawaiian Japanese, who have a high risk for colonic malignancy, the prevalence of adenomas is more than 50%.[50] on contrast, Japanese people residing in Japan have a low risk for colonic malignancy and polyps.[50] India is considered a low-prevalence region for colonic adenomas and colorectal malignancy.[51,52]

Fewer than 5% of Indian adults with colonic carcinoma harbor colonic adenomas.[51]

In a retrospective study published by Jose tony et al in 2006 from Calicut medical college, the incidence of colonic polyps in south Indian population group was found to be around 5%. The predominant histology of these polyps was adenoma and the most common site of polyp location was found to be left colon. The study was an original article named “The profile of colonic polyps in a south Indian population” published in INDIAN JOURNAL OF GASTROENTEROLOGY at 2007.

The low incidence rate of colorectal polyps in Indian population could be due to several factors including decreased genetic predisposition, high dietary fiber intake, low rate of awareness among public regarding the importance of screening colonoscopy, etc.

Although genetic predisposition clearly plays a role in colorectal carcinogenesis, diet and life-style factors also contribute. It is estimated that as much as a third to a half of colon cancer risk and a fourth to a third of distal colon adenoma risk might be avoidable by modification of dietary and life-style habits. For the most part, dietary factors that correlate with a predisposition to colon cancer also are associated with a risk for colonic adenomas. Factors that have each been correlated with an increased adenoma risk include excess dietary fat, excess alcohol intake, obesity, and cigarette smoking. Curiously, low calcium intake, despite

being associated with increased risk for colon cancer, does not appear to confer risk for adenoma (although calcium supplementation does seem to lower adenoma recurrences).

A variety of clinical circumstances have been associated with adenomatous polyps. Of the conditions discussed here, the predisposition to have or to develop adenomas is strongest for ureterosigmoidostomy, acromegaly, and Streptococcus bovis bacteremia. Patients with any of these three conditions should undergo a thorough colorectal examination and, in the former two conditions, periodic surveillance should be considered (although the frequency of such examinations is not well defined). As for the other conditions, either data are conflicting or the risk is not strong enough to recommend a policy of surveillance.

Role of colonoscopy in detection of colorectal adenomas

Colonoscopy is preferred to double-contrast barium enema examination for detecting adenomas because it has enhanced diagnostic accuracy as well as therapeutic capability. This diagnostic superiority has been demonstrated in studies of patients with known polyps as well as in symptomatic patients who have negative findings on proctosigmoidoscopic and barium enema examinations. Colonoscopy has become the preferred colon cancer screening test in many settings.

Despite its reputation as the gold standard for detecting adenomas, colonoscopy does have some limitations. Colonoscopy fails to reach the cecum in up to 10% of cases, it usually requires sedating the patient, and it carries a higher cost than FOBT, FIT, or sigmoidoscopy. Colonoscopy also can miss neoplasms, especially those located at flexures or behind folds. In general, adenomas that are missed tend to be small. Studies using a tandem colonoscopy design demonstrate adenoma miss rates of 0% to 6%, 12% to 13%, and 15% to 27% for adenomas larger than 1 cm, between 6 and 9 mm, and less than 6 mm, respectively. CT colonography reveals that colonoscopy can miss 12% to 17% of adenomas larger than 1 cm.

Given the concern about polyp miss rates, there has been increasing attention to quality measures for colonoscopy. Key measures of high-quality colonoscopy include adequacy of preparation, caecal intubation rate, withdrawal time, and adenoma detection rate. Inadequate preparation contributes to prolonged procedure times, decreased detection of lesions, and the need for repeat colonoscopy before recommended surveillance intervals. Colonoscopy is not considered complete unless caecal intubation is accomplished. The majority of screening colonoscopy studies reports a caecal intubation rate greater than 95%. Current guidelines suggest that caecal intubation rates should be greater than 90%

for all colonoscopies and greater than 95% in screening colonoscopies. Most screening colonoscopy studies report adenoma detection rates of 25% to 40%. Men have been consistently found to have a higher burden of adenomas than women. Current guidelines suggest that adenoma detection rates should be at least 15% in women and 25% in men.

A key factor in adenoma detection rate is colonoscopic withdrawal time. A large study examined the effect of withdrawal time in more than 7800 colonoscopies performed by 12 endoscopists. The adenoma detection rate was 28.3% among endoscopists with a withdrawal time of six minutes or more compared with 11.8% when the withdrawal time was shorter than six minutes. The respective detection rates for advanced adenomas were 6.4% and 2.6%; slower withdrawal time has been validated by the same investigators in a follow-up study of over 2300 colonoscopies. Current recommendations suggest that a withdrawal time of at least six minutes is necessary to maximize detection of adenomas. Continued emphasis on adhering to quality measures and detailed elucidation of the reasons lesions are missed can serve to improve colonoscopy further.

Insulin resistance and metabolic syndrome are known risk factors for colorectal adenomas. Non alcoholic fatty liver is a very common

associated condition in patients with insulin resistance and metabolic syndrome. There are few studies from western hemisphere trying to assess the association between Non alcoholic fatty liver and colorectal adenomas. Recently there have been some studies published from oriental countries exploring the possibility of association between colorectal adenoma and Non alcoholic fatty liver.

In a study published online March 17 in the Journal of Internal Medicine, the prevalence of early or precursor colorectal carcinoma lesions are higher among patients with NAFLD who underwent screening colonoscopy.

Andreas Stadlmayr et al evaluated the role of NAFLD as an independent risk factor for CRC. In this retrospective study data regarding 1,211 patients who underwent screening colonoscopy was collected The study group consisted of 603 males and 608 females. Average age of the study population was around 60 years. Increased echogenicity on ultrasound examination was used as criteria to diagnose NAFLD. Colorectal adenomas were categorized as tubular adenoma, advanced adenoma, or carcinoma.

Overall 367 males and 265 females in that study were found to have NAFLD. Significantly higher total rate of adenomas was present in

men and women who had NAFLD than individuals without NAFLD. Among male patients with NAFLD there was an increased prevalence of colorectal adenomas especially tubular adenomas as well as adenocarcinomas. The commonest site was rectum. In female patients with NAFLD there was an increased prevalence of colorectal adenomas especially tubular adenomas and commonest site is proximal colon. The difference between patients with normal ultrasonogram of liver and in patients with NAFLD after adjusting for age, race and other comorbidities was significant (odds ratio, 1.47).

Hence the author concluded that patients with NAFLD when undergoing screening colonoscopy have revealed significantly more CRC precursor lesions and early CRC compared to patients without NAFLD. So the author also suggests that detecting fatty liver on ultrasound should make us think about referral to screening colonoscopy.

In a similar study published in the Journal of gastroenterology and hepatology by Sang Tae Hwang et al, named as Relationship of Non-alcoholic Fatty Liver Disease to Colorectal Adenomatous Polyps, the authors concluded that the prevalence of NAFLD was 41.5% in the adenomatous polyp group and 30.2% in the control group. By multiple logistic regression analysis, NAFLD was found to be associated with an

increased risk of colorectal adenomatous polyps (odds ratio, 1.28; 95% confidence interval, 1.03–1.60). An increased risk for NAFLD was more evident in patients with a greater number of adenomatous polyps.

However in a recent study named Prevalence of colonic adenomas in patients with nonalcoholic fatty liver disease by Nadege T. Touzin et al published in Therapeutic advances in gastroenterology in 2011, have given different conclusion from the previous studies.

It was a retrospective cohort observational study with study group on 233 patients who underwent screening colonoscopies. The study was from Brooke Army Medical Center. Data was collected from November 2007 to March 2010. The study group tried to assess for the association between NAFLD and colonic adenomas. Biopsy-proven simple steatosis or nonalcoholic steatohepatitis (NASH) group were compared with a control group without fatty liver disease on sonographic imaging. Stratification was based on following parameters: race, body mass index (BMI), gender, and family history. The outcome was adjusted for variables which are known to be associated with increased risk of adenoma.

In this analysis the mean age was 54.7±6.0 years. Population comprised of 62.7% White, and 18.5% Hispanic, slightly lesser

population of blacks with 13.7%, African American, and 5.2% other. The mean BMI was 29.7±5.8. The control group had prevalence of colonic adenomas of around 25.1%. Around 24.4% patients in the NAFLD group had colonic adenomas. (p value1.00). After adjusting for confounders like, BMI, race and family history, no significant difference was found (p value - 0.33). However, the ultrasound-negative patients ranked lower in the number of adenomas per person (p value 0.016).

There was no difference in the prevalence of colonic adenomas when comparing the NAFLD group who had undergone colonoscopy with a group of control patients without NAFLD who had undergone colonoscopy. However, patients with negative ultrasounds appeared to have a lower polyp burden.

AIM AND OBJECTIVES OF THE STUDY

1. To know the prevalence of colorectal adenomas in patients with Non Alcoholic Fatty Liver Disease.

2. To study the colonoscopy findings in patients with Non Alcoholic Fatty Liver Disease.

3. To assess the risk of colorectal adenomas in Patients with Non Alcoholic Fatty Liver Disease and Metabolic syndrome

MATERIALS AND METHODS

The study included out patients who attended the outpatient department in our Institution (Department of Digestive Health and Diseases, Government Peripheral Hospital, Anna Nagar, Chennai -102) which is a major tertiary care Centre for liver diseases. Patients were included in this study after their Willingness to undergo necessary investigations. Informed written consent was taken before the enrolment in this study. The period of study is from May 2011 to October 2011.

Inclusion criteria : Age 40 -70 years.

Patients with bright liver on ultrasound examination Suggestive of fatty liver.

Patients with normal liver on ultrasound examination as control group.

Exclusion criteria : Age below 40 years and above 70 years.

Patients with Infectious,immunological, hereditary, alcoholic liver diseases, Wilson disease, Hemochromatosis, Patients with history of colorectal malignancies, Family history of GI polyposis, History of alcohol intake. Patients with history of drug induced liver injury.

Study methodology : Study is a Prospective case control study

Population consist of patients assessed in the institute satisfying the

inclusion and exclusion criteria during the period from May 2011 to October 2011.

Study material : History

Clinical features

Investigations.

After careful screening for exclusion criteria 129 patients were included in the study after obtaining informed consent. Patients who came for master health checkup and healthy relatives of patients, with normal liver on ultrasonogram and normal liver function tests were included as control group after obtaining informed consent to undergo screening colonoscopy.

Patients were examined clinically and their abdominal girth measurements were taken midway between umbilicus and lower costal margin. Blood pressure measured in sitting posture in both upper limbs.

Obesity is defined as the presence of waist circumference more than 40 inches in men and more than 35 inches in women according to the ATP III guidelines of national cholesterol education program.

Presence of blood pressure more than 130mmHg systolic and 85mmHg diastolic was taken as significant as it forms a part of metabolic syndrome according to the ATP III guidelines of national cholesterol education program.

Presence of fasting blood glucose more than 110 mg% is considered significant as it forms a part of metabolic syndrome according to the ATP III guidelines of national cholesterol education program.

All patients were subjected to fasting lipid profile assessment. Presence of fasting serum triglyceride more than 150mg% is considered significant. Similarly presence of serum HDL values less than 40mg% for men and less than 50mg% for women is considered significant as it forms a part of metabolic syndrome according to the ATP III guidelines of national cholesterol education program. Patients were diagnosed to have metabolic syndrome if they satisfy the criteria for metabolic syndrome according to ATP III guidelines of National Cholesterol Education Program. According to this presence of any three of the five following parameters is necessary to diagnose metabolic syndrome.

1. Fasting blood glucose ≥110 mg%

2. Waist circumference ≥40 inches in men and ≥35 inches in women.

3. Blood pressure ≥130mmHg systolic and ≥85mmHg diastolic.

4. Fasting serum triglyceride ≥150mg%.

5. Serum HDL values ≤40mg% for men and ≤50mg% for women.

All patients were subjected to screening ultra sonogram of abdomen. Ultra sonogram was performed by a qualified and experienced ultrasonologist. Patients in whom echogenic bright liver was present in the absence of viral, immunological, alcoholic and metabolic liver diseases were presumed to have non alcoholic fatty liver. This method is commonly used in clinical practice as well as in epidemiological studies for diagnosing Non alcoholic fatty liver disease. The term Presumed NAFLD is used in such studies to describe the condition.[53]

Those with normal echogenicity of liver in ultra sonogram and satisfying the inclusion and exclusion criteria are included into control group.

In patients with presumed Non alcoholic fatty liver disease with coexisting elevation of transaminases like AST and ALT were subjected

to liver biopsy after obtaining informed consent from the patients. Histological grading of Non alcoholic liver disease in these patients was carried out using the classification by matteoni et al[54].

(1) simple steatosis (2) steatosis with inflammation alone, (3) steatosis with inflammation and ballooning, and (4) steatosis with inflammation and fibrosis

After bowel preparation all these patients were subjected to complete colonoscopy up to caecum. Careful screening for the presence of polyps and neoplasia was done in all these patients. Biopsies were taken from the polyps. The size of the polyps was noted as less than one cm or greater than one cm. Site of the polyps as well as the number of polyps were also noted.

Histopathological assessment of the biopsies taken from the polyps was collected and the type of polyp is noted as whether hyperplastic, inflammatory, hammartomatous or adenomatous polyps.

STATISTICAL ANALYSIS

The statistical analysis was performed with the Windows SPSS program ver. 15.0. The statistical results are presented as the mean ± standard deviation or percentages. Statistical analyses included an independent sample Student's *t*-test and the χ^2-test (for categorical variables). The relationship of NAFLD with the presence of adenomatous polyps was assessed by multiple logistic regression analysis after adjustment for independent variables, including age, sex, hypertension, diabetes, metabolic syndrome and NAFLD. Each odds ratio (OR) is presented together with its 95% confidence interval (CI). $P < 0.05$ was considered statistically significant.

RESULTS

About 129 patients were included in this study. Age ranged from 40 year to 70 years. Average age of patients in this study was 54.77 years.

Table1. Age distribution in the study population.

	N	Minimum	Maximum	Mean	Std. Deviation
Age in years	129	40	70	54.77	8.684
Valid N (listwise)	129				

Among the study population 69 patients were found to have Non alcoholic fatty liver and 60 patients were found to have normal liver based on ultra sonogram abdomen and biochemical parameters. Patients with Non alcoholic fatty liver comprised 53.5% of the study population.

Table2. Number of NAFLD patients and control population

NAFLD	Frequency	Percent	Valid Percent	Cumulative Percent
Absent	60	46.5	46.5	46.5
Present	69	53.5	53.5	100.0
Total	129	100.0	100.0	

Among the study population the average age of control group was 56.13 years and the average age of NAFLD group was 53.58 years.

Table 3. Age distribution in NAFLD and CONTROL group

	Patient group	N	Mean	Std. Deviation	Std. Error Mean
Age in years	CONTROL	60	56.13	8.355	1.079
	NAFLD	69	53.58	8.849	1.065

Among the study population 71 were men and 58 were women.

Table4. Sex distribution in the study population.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Male	71	55.0	55.0	55.0
	Female	58	45.0	45.0	100.0
	Total	129	100.0	100.0	

Among the study population 51 patients were diagnosed to have metabolic syndrome which comprised about 39.5% of the study population.

Table5. Distribution of metabolic syndrome in the study group.

Metabolic syndrome	Frequency	Percent	Valid Percent	Cumulative Percent
Absent	78	60.5	60.5	60.5
Present	51	39.5	39.5	100.0
Total	129	100.0	100.0	

Among the patients with NAFLD group 30 patients had metabolic syndrome comprising about 43.5% of NAFLD group. Whereas in the control group, metabolic syndrome was present in 21 patients comprising about 35% of patients with control group.

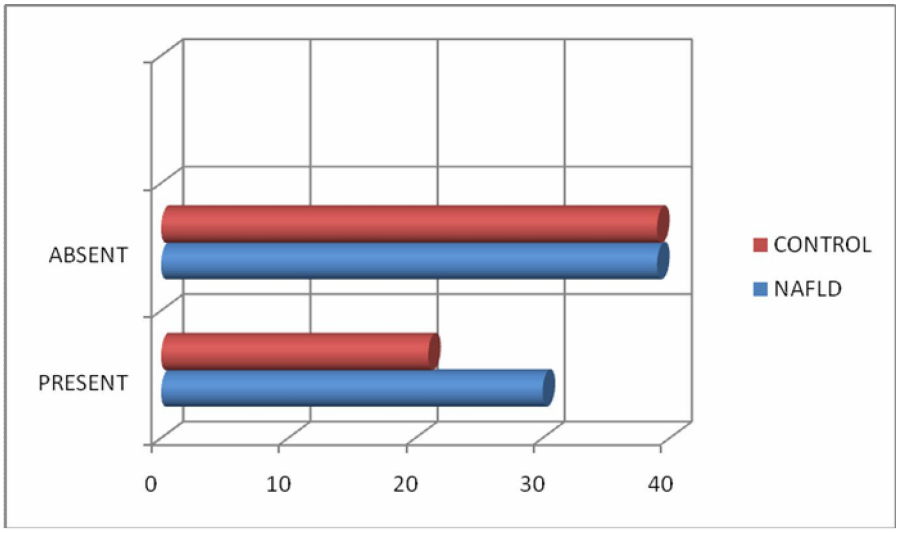

Figure depicting the prevalence of metabolic syndrome in NAFLD group and CONTROL group.

Table6. Frequency of metabolic syndrome in NAFLD and control groups

			Metabolic Syndrome		Total
			Absent	Present	
USG FATTY LIVER	ABSENT	Count	39	21	60
		USG	65.0%	35.0%	100.0%
		% within Metabolic Syndrome	50.0%	41.2%	46.5%
	PRESENT	Count	39	30	69
		% within USG	56.5%	43.5%	100.0%
		% within Metabolic Syndrome	50.0%	58.8%	53.5%
Total		Count	78	51	129
		% within USG	60.5%	39.5%	100.0%
		% within Metabolic Syndrome	100.0%	100.0%	100.0%

In the study population impaired fasting glucose was present in 48% of the patients.

Table7. Frequency of impaired fasting glucose in study population.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Absent	67	51.9	51.9	51.9
	Present	62	48.1	48.1	100.0
	Total	129	100.0	100.0	

In the study population BP ≥130/85 mm HG was present in 47.3% population. There was no significant difference in NAFLD group and control group.

Table8. Frequency of elevated BP in the study population.

BP≥ 130/85 mHG	Frequency	Percent	Valid Percent	Cumulative Percent
Absent	68	52.7	52.7	52.7
Present	61	47.3	47.3	100.0
Total	129	100.0	100.0	

Among the study population hypertriglyceridemia was present in 31patients comprising about 24%. There was no significant difference in NAFLD group and control group.

Table9. Frequency of Hypertryglyceridemia in study population

Hypertryglyceridemia		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Absent	98	76.0	76.0	76.0
	Present	31	24.0	24.0	100.0
	Total	129	100.0	100.0	

Among the study population 64(49.6%) patients had obesity based on the waist circumference. There was no significant difference in NAFLD group and control group.

Table10. Frequency of obesity in study population

obesity	Frequency	Percent	Valid Percent	Cumulative Percent
Absent	65	50.4	50.4	50.4
Present	64	49.6	49.6	100.0
Total	129	100.0	100.0	

Among the study population 39(30.2%) patients had low HDL cholesterol levels.

Table11. Frequency of low HDL cholesterol in study population.

Low HDL cholesterol		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Absent	90	69.8	69.8	69.8
	Present	39	30.2	30.2	100.0
	Total	129	100.0	100.0	

Among the study population only four patients had elevation in AST/ALT levels two folds above base line. All these four patients also had fatty liver on ultrasonogram. Only these four patients were subjected to liver biopsy after obtaining informed consent. In all other patients liver biopsy could not be done due to ethical reasons.

Table12. Frequency of elevated transaminases in study population.

Elevated transaminases		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Absent	125	96.9	96.9	96.9
	Present	4	3.1	3.1	100.0
	Total	129	100.0	100.0	

Histological assessment of the liver biopsy specimen was done and staging was done in four patients. None of them had cirrhosis while two patients had steatosis with non specific lobular inflammation. Two patients had steatosis with lobular inflammation and fibrosis.

In all the patients screening colonoscopy up to cecum was successfully completed without any complications and careful screening for the presence of any polyps was done. In the presence of any polyp the size of the polyp, number of polyps and the location of polyps are noted.

In the study population 11 patients were found to have polyps in the screening colonoscopy which formed about 8.5% of the study population. Rest of the patients did not have any significant finding in the colonoscopy.

Table13. Frequency of polyps on colonoscopy in the study population.

POLYP	Frequency	Percent	Valid Percent	Cumulative Percent
Absent	118	91.5	91.5	91.5
Present	11	8.5	8.5	100.0
Total	129	100.0	100.0	

Among the 11 patients one patient had three polyps and three patients had 2 polyps each and rest of them had one polyp.

Table14. Polyp burden in the study population.

Number of polyps	Frequency	Percent	Valid Percent	Cumulative Percent
0	118	91.5	91.5	91.5
1	7	5.4	5.4	96.9
2	3	2.3	2.3	99.2
3	1	.8	.8	100.0
Total	129	100.0	100.0	

Over all the distribution of polyps was predominantly on the left colon.

Table15. Location of polyps

Location of polyps	Frequency	Percent	Valid Percent	Cumulative Percent
NO POLYP	122	94.6	94.6	94.6
LEFT COLON	6	4.7	4.7	99.2
RT COLON	1	.8	.8	100.0
Total	129	100.0	100.0	

In patients with NAFLD the polyps were present in 8.7% patients and in control group it was 8.3%. This difference was not statistically significant.

Table16. Prevalence of polyps in NAFLD group and CONTROL group.

			polyp		Total
			Absent	**Present**	
Presumed NAFLD	Absent	Count	55	5	60
		% within USG	91.7%	8.3%	100.0%
		% within COLONOSCOPY	46.6%	45.5%	46.5%
	Present	Count	63	6	69
		% within USG	91.3%	8.7%	100.0%
		% within COLONOSCOPY	53.4%	54.5%	53.5%
Total		Count	118	11	129
		% within USG	91.5%	8.5%	100.0%
		% within COLONOSCOPY	100.0%	100.0%	100.0%

In all these patients biopsy from the polyp was taken and histo pathological assessment of polyps was done. Nine out of the 11 patients were found to have tubular adenomas with no dysplasia and two patients were found to have hyperplastic polyps. The frequency of adenomas in the study population was about 7%.

Table17. Histopathology of polyps in the study population.

Polyp histology	Frequency	Percent	Valid Percent	Cumulative Percent
Absent	118	91.5	91.5	91.5
Adenoma	9	7.0	7.0	98.4
Others	2	1.6	1.6	100.0
Total	129	100.0	100.0	

Among the study group the prevalence of adenoma in NAFLD group was around 7.2% and in control population the prevalence was about 6.8%. There was no statistically significant difference in the prevalence of colonic adenomas in both the groups.

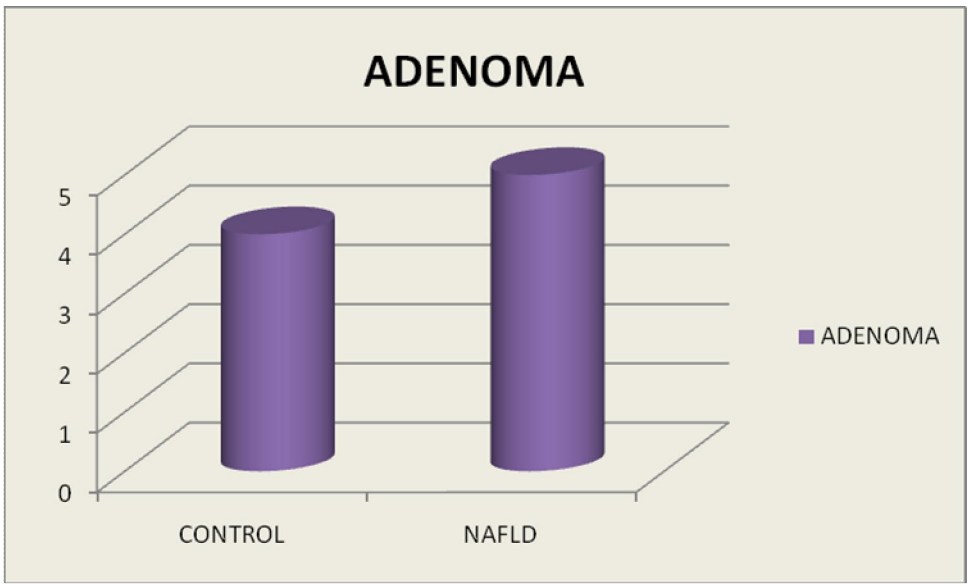

Figure showing the number of adenomas in NAFLD and CONTROL groups

Table18. Prevalence of adenomas in NAFLD and CONTROL group

			POLYP HPE			Total
			Absent	**Adeoma**	**Others**	
USG BRIGHT LIVER	Absent (CONTROL)	Count	55	4	1	60
		% within USG	91.7%	6.7%	1.7%	100.0%
		% within POLYP HPE	46.6%	44.4%	50.0%	46.5%
	Present (NAFLD)	Count	63	5	1	69
		% within USG	91.3%	7.2%	1.4%	100.0%
		% within POLYP HPE	53.4%	55.6%	50.0%	53.5%
Total		Count	118	9	2	129
		% within USG	91.5%	7.0%	1.6%	100.0%
		% within POLYP HPE	100.0%	100.0%	100.0%	100.0%

Among the patients with adenoma the average age was 60.44 years around 6 years greater than those without adenomas. The age difference was statistically significant (P value 0.037), based on t- test for equality of means.

Table19. Age distribution in patients with and with out adenomas.

	ADENOMA	N	Mean	Std. Deviation	Std. Error Mean
Age in years	Absent	118	54.21	8.660	.797
	Present	9	60.44	6.616	2.205

Among the study group the prevalence of colorectal adenoma was more common among patients with metabolic syndrome than others and the difference was statistically significant. All the patients with colorectal adenomas also had metabolic syndrome.(p value 0.047)

Table20. Colorectal adenomas in patients with and without metabolic syndrome.

			POLYP HPE			Total
			Absent	Adenoma	Others	
Metabolic Syndrome	Absent	Count	76	0	2	78
		% within Metabolic Syndrome	97.4%	.0%	2.6%	100.0%
		% within POLYP HPE	64.4%	.0%	100.0%	60.5%
	Present	Count	42	9	0	51
		% within Metabolic Syndrome	82.4%	17.6%	.0%	100.0%
		% within POLYP HPE	35.6%	100.0%	.0%	39.5%
Total		Count	118	9	2	129
		% within Metabolic Syndrome	91.5%	7.0%	1.6%	100.0%
		% within POLYP HPE	100.0%	100.0%	100.0%	100.0%

The colorectal adenoma burden was found to be higher in the NAFLD group when compared with control group.

There was a statistically significant increase in the adenoma burden in patients with NAFLD group compared with the control group based on t- test for equality of means. P value (0.027).

Table21. Adenoma burden in relation to presumed NAFLD

	USG	N	Mean	Std. Deviation	Std. Error Mean
No. of polyps	Absent	4	1.00	.000	.000
	Present	5	2.00	.707	.316

DISCUSSION

Non alcoholic fatty liver is a new age epidemic which has started to rise in incidence for last two decades. NAFLD which is a hepatic manifestation of metabolic syndrome and metabolic syndrome seems to increase the risk of colorectal cancer, as shown in studies [Colangelo et al. 2002; Trevisan et al. 2001]. Insulin resistance is the common under lying mechanism for both entities [Pais et al. 2009]. Perhaps the same factors that lead to metabolic syndrome, also has a distinct role in carcinogenesis[55].

Adiponectin is decreased in obese and diabetics or in patients with insulin resistance. This leads to increased insulin levels due to marked insulin resistance, which in turn causes increase in insulin growth factor-1 (IGF-1) [Kaaks et al. 2000]. Adiponectin inhibits tumor necrosis factor alpha (TNF-a), which plays a role in tumor cell proliferation and angiogenesis [Ferroni et al. 2007; Rose et al. 2004].

In a study by Ferroni and colleagues [Ferroni et al. 2007], there was an inverse association between adiponectin levels to colonic tumor stage and adiponectin levels independently seem to predict cancer recurrence [Stattinet al. 2004]. Insulin binds to IGF-1 receptors and as very important role in modifying cell proliferation, apoptosis and also

increased levels of vascular endothelial growth factor, an angiogenic factor, that supports cancer growth [Grimberg and Cohen, 2000; Warren et al. 1996].

Although we need more studies to find out how exactly the risk of colorectal adenomas is increased in patients with metabolic syndrome, an association is somewhat obvious and clinically recognizable[55].

There are several studies from western literature analyzing the prevalence of colorectal adenomas in patients with Non alcoholic fatty liver disease. Some of them have found an increased prevalence of colorectal adenomas in patients with Non alcoholic liver disease leading to the suggestion that patients with Non alcoholic fatty liver disease should be considered for screening colonoscopy.

In the study by Sang Tae Hwang et al, the prevalence of NAFLD was 41.5% in the adenomatous polyp group and 30.2% in the control group. By multiple logistic regression analysis, NAFLD was found to be associated with an increased risk of colorectal adenomatous polyps (odds ratio, 1.28; 95% confidence interval, 1.03–1.60). An increased risk for NAFLD was more evident in patients with a greater number of adenomatous polyps. [56]

In a similar study by Stadlmayr A et al, the author concluded that Patients with NAFLD had significantly more CRC precursor lesions and early CRC. This elevated risk is independent from other manifestations of Insulin Resistance. These findings seem to favor referral to screening colonoscopy in patients with NAFLD.[57]

However many other studies performed at different centers later seem to show results that are different from the previously discussed studies. In a study by Wong et al, the prevalence of colorectal adenomas is equal in patients with non alcoholic fatty liver and control group. The prevalence was slightly higher in patients with non alcoholic steatohepatitis patients.

The author concluded a high prevalence of colorectal adenomas and advanced neoplasms is associated with non alcoholic steatohepatitis. The right sided colon is a more common site for adenomas. Colorectal cancer screening is strongly indicated in this high risk group. After demographic and metabolic factors were adjusted, non-alcoholic steatohepatitis still remained a significant factor in increased incidence of adenomas (adjusted OR 4.89, 95% CI 2.04 to 11.70) and advanced neoplasms (OR 5.34, 95% CI 1.92 to 14.84). However, the prevalence of

adenomas and advanced neoplasms was not different in patients with simple steatosis and control subjects.[58]

In a study by Nadege Touzin et al, the author found out that the prevalence of adenomas in both NAFLD group and control was similar. 25.1% of patients in control group had colorectal adenomas and where as it was 24.4% in the NAFLD group including simple steatosis and NASH (p value 1.00). After adjusting for known confounders like, BMI, race and family history, not much significant difference (p value 0.33) could be found. However, the ultrasound-negative patients had fewer adenomas per person (p value 0.016). So in this study, the prevalence of colonic adenomas in the NAFLD group and in the control patients without NAFLD was not significantly different. However, patients with negative ultrasounds appeared to have a lower polyp burden.[55]

The increased risk of colorectal adenomas in patients with metabolic syndrome was described by Giovannucci E in a review article named Metabolic syndrome, hyperinsulinemia, and colon cancer: a review.[59]

In India there is no study to analyze the association between non alcoholic fatty liver and colorectal adenomas. In this study the prevalence of colorectal adenoma in patients with non alcoholic fatty liver disease and normal population was assessed. In this case controlled study the prevalence of colorectal adenoma over all was around 7%. The prevalence of colorectal adenoma in patients with presumed non alcoholic fatty liver group was around 7.2% and on control group it was around 6.8%. The difference was not statistically significant.

However the polyp burden in patients with presumed non alcoholic fatty liver is twice that of the control group with p value of 0.027. In patients with non alcoholic fatty liver disease group the number of polyps is 2 and above where as in control group usually the number of polyp is one.

Irrespective of the presence or absence of fatty liver, the patients with colorectal adenoma had metabolic syndrome. Metabolic syndrome seems to be the strong risk factor of colorectal adenoma.

Average age of patients with colorectal adenoma in this study is about 60.5 years, which is 6 years greater than the average age of patients without colorectal adenoma.

In this study age and metabolic syndrome are the independent risk factors for colorectal adenomas where as non alcoholic fatty liver disease is not an independent risk factor. Non alcoholic fatty liver seems to increase the polyp burden in patients with colorectal adenomas.

The limitations in this study are small sample size of the study population and the lack of histological diagnosis and grading of fatty liver. The diagnosis of non alcoholic fatty liver was made based on the presence of bright liver on ultrasound with absence of evidence for any other liver disease or systemic disease predisposing to fatty liver. Since the ultrasound has poor sensitivity to detect fatty liver in obese patients, this could impair the study outcome. Liver biopsy could not be performed in all patients because of ethical reasons. Liver biopsy was done in our patients in whom there was an elevation in the AST/ALT levels. In these patients two had steatohepatitis and two had fibrosis. However in these patients there was no colorectal adenomas and hence the histology does not seem to be a factor in prevalence of colorectal adenoma.

Over all prevalence of colorectal adenoma in this study population was around 7% which is slightly higher than what was found in previous studies. This could probably due to the fact that the average age of patients in the study population was 54.77% and patients belonged to

urban population. In an article published by Jose Tony et al, the prevalence of polyps was around 5.1% most of them being adenoma. This article titled “Profile of colonic polyps in a southern Indian population” was published in Indian Journal of Gastroenterology 2007 Vol 26 May - June 129.

The relationship between metabolic syndrome and colorectal neoplasia is well established and the underlying reason for this has been increased insulin resistance in patients with metabolic syndrome. Metabolic syndrome is a manifestation of insulin resistance which predisposes to several malignancies. In this study all the patients who were diagnosed to have colorectal adenoma also had metabolic syndrome. There was a statistically significant association between colorectal adenoma and metabolic syndrome.(p value 0.04)

Age of patients in this study also showed statistically significant difference among the patients with colorectal adenoma and patients without colorectal adenoma. The average age of patients with colorectal adenoma was about 60.55 years which was 6 years greater than the average age of rest of the study group.

CONCLUSIONS

1. Non alcoholic fatty liver disease is not an independent risk factor for colorectal adenomas.

2. Non alcoholic fatty liver disease may increase the polyp burden in patients with colorectal adenomas.

3. Metabolic syndrome increases the risk of colorectal adenoma irrespective of the presence or absence of Non alcoholic fatty liver.

4. Screening colonoscopy is advisable in patients with Metabolic syndrome.

5. Colorectal adenomas seem to occur after the age of 60 years.

PROFOMA

NAME

AGE

SEX

IP NO

SOCIO ECONOMIC STATUS

ADDRESS

CHIEF COMPLAINTS

ABD PAIN

ALTERED BOWEL HABITS

WT LOSS

JAUNDICE

MALENA

PAST HISTORY

DIABETES MELLITUS

HYPERTENSION

LIVER DISEASE

DRUG HISTORY AND ALCOHOL INTAKE

FAMILY HISTORY

GI

MALIGNANCY/POLYPOSIS/LIVER DISEASE

GENERAL EXAMINATION

BMI WAIST

CIRCUMFERENCE

BP

ANAEMIA

JAUNDICE

HEPATOMEGALY

ABDOMINAL MASS

ASCITES

PER RECTAL EXAMINATION

LIVER FUNCTION TEST S.BILIRUBIN TOTAL

DIRECT

AST ALT

SAP

SERUM PROTEINS

BLOOD SUGAR F PP

SERUM LIPID PROFILE TOTAL CHOLESTEROL

LDL HDL TGL

VLDL

USG ABDOMEN

COLONOSCOPY

HISTOPATHOLOGICAL EXAMINATION of Liver biopsy

HISTOPATHOLOGICAL EXAMINATION of colonic polyp

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MASTER CHART

S.No	NAME	AGE	SEX	IMPAIRED FASTING GLUCOSE	BP≥130/ 85mmHG	HYPERTRIGL-YCERIDEMIA	OBESITY	LOW HDL	METABOLIC SYNDROME	OT/PT ELEVATION	USG BRIGHT LIVER	LIVER BX	POLYP	NUMBER OF POLYPS	POLYP HPE	POLYP SIZE	POLYP LOCATION
1	CHENGUTUVAN	66	M	1	1	0	1	1	1	0	1	0	1	2	1	1	1
2	MURUGESA PANDIAN	70	M	1	0	1	1	0	1	0	1	0	1	3	1	1	1
3	RAVI	56	M	1	1	0	1	0	1	0	1	0	1	2	1	1	2
4	BHAGYAM	52	F	1	1	1	1	0	1	0	1	0	1	1	1	2	1
5	SARAVANAMUTHU	53	M	0	1	0	1	1	1	0	1	0	1	2	1	2	1
6	SENGUTTUVAN	53	M	0	0	0	0	1	0	0	1	0	0	0	0	0	0
7	AYANNAR	55	M	0	1	0	0	1	0	0	1	0	1	1	2	0	1
8	KUMARAVEL	40	M	1	0	0	0	0	0	0	1	0	0	0	0	0	0
9	BHUVANESHWARI	41	F	0	1	0	0	0	0	0	1	0	0	0	0	0	0
10	NALLASIVAM	43	M	0	0	0	1	0	0	0	1	0	0	0	0	0	0
11	NAGARAJ	64	M	0	1	1	1	0	1	0	1	0	0	0	0	0	0
12	RAJA	40	M	0	1	1	1	1	1	0	1	0	0	0	0	0	0
13	KOTHANDAM	51	M	1	0	0	1	1	1	0	1	0	0	0	0	0	0
14	PRAKASAM	53	M	1	0	0	1	1	1	0	1	0	0	0	0	0	0
15	RAJA	46	M	0	1	1	1	1	1	0	1	0	0	0	0	0	0
16	RADHA	53	F	1	1	0	1	0	1	0	1	0	0	0	0	0	0
17	MANIVANNAN	51	M	0	1	0	1	1	1	0	1	0	0	0	0	0	0
18	KOKILA	43	F	1	1	0	0	0	1	0	1	0	0	0	0	0	0
19	MALA	45	F	1	1	0	1	1	1	0	1	0	0	0	0	0	0
20	VEDHAM	61	F	0	1	1	1	1	1	0	1	0	0	0	0	0	0
21	RADHA	68	F	1	1	0	0	1	1	0	1	0	0	0	0	0	0
22	VEMBU	60	M	0	1	1	1	1	1	0	1	0	0	0	0	0	0
23	LAKSMI	51	F	0	1	1	0	0	0	0	1	0	0	0	0	0	0
24	RAVI	40	M	0	1	1	1	1	1	0	1	0	0	0	0	0	0
25	AMBIKA DEVI	65	F	1	1	1	0	0	1	0	1	0	0	0	0	0	0
26	MUTHU	52	M	0	1	0	1	0	0	0	1	0	0	0	0	0	0
27	THENDRAL	43	M	1	1	1	1	0	1	0	1	0	0	0	0	0	0
28	RANI	48	F	0	0	1	1	0	0	0	1	0	0	0	0	0	0
29	ANJALAI	46	F	0	1	1	1	1	1	0	1	0	0	0	0	0	0
30	AMMU	59	F	1	0	1	1	0	1	0	1	0	0	0	0	0	0
31	NARASHIMAN	51	M	1	1	0	0	1	1	0	1	0	0	0	0	0	0
32	MEERA BAI	70	F	0	1	0	1	0	0	0	1	0	0	0	0	0	0
33	ISMAIL	51	M	1	1	0	0	1	1	0	1	0	0	0	0	0	0
34	ISAAC	57	M	1	0	0	1	0	0	0	1	0	0	0	0	0	0
35	KALLIMUTHU	61	m	1	0	0	1	1	1	0	1	0	0	0	0	0	0
36	MUNIAN	50	M	1	1	0	0	1	1	0	1	0	0	0	0	0	0
37	ABDULLAH	68	M	1	0	0	1	0	0	0	1	0	0	0	0	0	0
38	MATHIMALAR	55	F	1	0	1	1	0	1	0	1	0	0	0	0	0	0
39	THANGAM	41	F	1	0	1	0	0	0	0	1	0	0	0	0	0	0

40	MUTHALAGU	49	F	1	0	1	0	0	0	0	1	0	0	0	0	0	0	0
41	RANGARAJAN	63	M	0	1	1	1	1	1	1	1	1	0	0	0	0	0	0
42	THANAM	40	F	1	1	1	1	0	1	1	1	2	0	0	0	0	0	0
43	VENDA	44	F	0	1	1	1	0	1	1	1	2	0	0	0	0	0	0
44	MANIKANDAN	47	M	1	0	0	0	0	0	1	1	2	0	0	0	0	0	0
45	IYANAR	50	M	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
46	JOHNSON	60	M	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
47	RATHIMEENA	62	F	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0
48	MINNALKODI	59	F	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
49	MUNIAMMAL	52	F	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
50	RAJI	42	F	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
51	KALEEL	50	M	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
52	KRISHNAVENI	67	F	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
53	GAJENDRAN	66	M	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
54	BALAIAH	54	M	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0
55	ROSEMARY	40	F	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
56	RAJESWARI	43	F	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
57	JAMUNA	44	F	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
58	JANSI	49	F	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
59	ARULANANDAM	59	M	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
60	PUGALENDI	70	M	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
61	PITCHAMANI	51	M	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
62	PARIMALA	58	F	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
63	JAMUNARANI	70	F	1	0	0	0	1	0	0	1	0	0	0	0	0	0	0
64	BAJAN LAL	54	M	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
65	TARA BAI	60	F	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0
66	THANGAMAL	65	F	1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
67	THANIGAI	49	M	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
68	MUKUNDAN	58	M	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0
69	JEELANI BEE	50	F	0	1	0	1	0	0	0	1	0	0	0	0	0	0	0
70	RAGURAM	69	M	1	1	1	1	0	1	0	0	0	1	1	1	1	0	
71	MATHANGI	59	F	1	1	0	1	1	1	0	0	0	1	1	1	1	0	
72	MUTHU	69	M	0	0	0	1	0	0	0	0	0	1	1	2	1	0	
73	MANIMARAN	58	M	1	1	0	1	0	1	0	0	0	1	1	1	1	0	
74	JAYASHREE	61	F	1	1	1	1	0	1	0	0	0	1	1	1	1	1	
75	SHANTHI	49	F	0	1	0	1	1	1	0	0	0	0	0	0	0	0	
76	KOSHI	54	M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
77	RAMIYAH	60	M	0	0	0	1	0	0	0	0	0	0	0	0	0	0	
78	SARGUNAM	40	M	0	1	0	0	0	0	0	0	0	0	0	0	0	0	
79	NEELAMEGAM	45	F	1	0	0	1	0	0	0	0	0	0	0	0	0	0	
80	POOVAMAL	65	F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
81	KUPPAN	58	M	1	0	0	0	1	0	0	0	0	0	0	0	0	0	
82	THARANI	54	M	0	0	0	0	1	0	0	0	0	0	0	0	0	0	
83	SUDHA	48	F	0	1	1	0	0	0	0	0	0	0	0	0	0	0	
84	MARI	57	F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
85	KANAMMAL	60	F	1	0	0	0	0	0	0	0	0	0	0	0	0	0	

86	HARIHARAN	55	M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
87	NISHA	40	F	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
88	LAL KISHAN	50	M	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0
89	JAYANTHI	52	F	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
90	GANGA	61	F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
91	BALASHANKAR	40	M	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0
92	PRADEEP	40	M	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0
93	PANDIYAN	48	M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
94	POTHIYAPPAN	58	M	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
95	AKILANDESWARI	60	F	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
96	ARUMAUGAM	63	M	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
97	SHANMUGAM	70	M	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
98	VASUKI	68	F	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0
99	SEETHA	51	F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
100	STALIN	50	M	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
101	GIRIJA	61	F	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
102	KUMARI	68	F	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
103	KANCHANA	70	F	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
104	VAIRAVAN	63	M	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
105	AMUDAN	51	M	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
106	JUSTIN PAL	42	M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
107	JABARAJ	47	M	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
108	GANAPATHY	50	M	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0
109	GUGAN	48	M	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
110	VENKATESAN	55	M	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
111	MURALIDARAN	60	M	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
112	SARITHA	62	F	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
113	THENMOZHI	49	F	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0
114	NAGARJUNAN	50	M	1	0	1	1	1	1	0	0	0	0	0	0	0	0	0
115	RANI	59	F	0	1	1	1	1	1	0	0	0	0	0	0	0	0	0
116	MARY	61	F	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0
117	ARULSELVAN	64	F	0	1	0	1	1	1	0	0	0	0	0	0	0	0	0
118	DEVI	66	F	0	1	1	1	0	1	0	0	0	0	0	0	0	0	0
119	RASU	56	M	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0
120	MARIKOLUNDU	49	F	1	1	1	1	0	1	0	0	0	0	0	0	0	0	0
121	MUMTAZ	48	F	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0
122	ALAGESAN	50	M	1	0	0	1	1	1	0	0	0	0	0	0	0	0	0
123	GANESAN	70	M	0	1	0	1	1	1	0	0	0	0	0	0	0	0	0
124	ABDUL RAZAK	49	M	0	1	0	1	1	1	0	0	0	0	0	0	0	0	0
125	CHINNAIAH	58	M	1	1	0	1	1	1	0	0	0	0	0	0	0	0	0
126	DHARMALINGAM	60	M	0	1	0	1	1	1	0	0	0	0	0	0	0	0	0
127	DHARANI	62	F	1	0	1	1	0	1	0	0	0	0	0	0	0	0	0
128	ILAYARAJA	67	M	1	1	0	1	0	1	0	0	0	0	0	0	0	0	0
129	ISAKI	61	M	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0

POLYP SIZE	<1 CM =1	>1 CM =2	ABSENT-0			
USG BRIGHT LIVER	ABSENT-0	PRESENT-1				
POLYP LOCATION	LEFT COLON-1	RT COLON-2	NO POLYP-0			
LIVER BX	NOT DONE-0		STG1-1	STG2-2	STG3-3	STG4-4
OT/PT ELEVATION	ABSENT-0	PRESENT-1				
NUMBER OF POLYPS	ABSENT-0					
POLYP HPE	ABSENT-0	ADENOMA-1	OTHERS-2			
POLYP	ABSENT-0	PRESENT-1				
IMPAIRED FASTING GLUCOSE	ABSENT-0	PRESENT-1				
BP≥130/85mmHG	ABSENT-0	PRESENT-1				
HYPERTRIGLYCERIDEMIA	ABSENT-0	PRESENT-1				
LOW HDL	ABSENT-0	PRESENT-1				
OBESITY	ABSENT-0	PRESENT-1				
METABOLIC SYNDROME			ABSENT-0	PRESENT-1		